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Title Page

Title: Neurological rarity - Ovarioleukodystrophy due to *EIF2B5* mutations

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ABSTRACT

Ovarioleukodystrophy – the co-occurrence of leukodystrophy and premature ovarian failure – is a rare presentation which is now recognised to be part of the clinical spectrum of vanishing white matter disease. We present the case of a lady with known seizures and neuroimaging changes consistent with leukoencephalopathy who presented with non-convulsive status epilepticus following initiation of hormone replacement therapy in the context of premature ovarian failure. Genetic testing confirmed she is a compound heterozygote for *EIF2B-5* mutations; the gene encodes a subunit of eukaryotic translation initiation factor 2B. Mutations in *EIF2B1-5* result in vanishing white matter disease. We highlight the importance of careful systemic review when investigating leukoencephalopathy and present a brief literature review of ovarioleukodystrophy.

MAIN TEXT

INTRODUCTION

The finding of leukoencephalopathy on neuroimaging requires consideration of a broad range of differential diagnoses including Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL), lysosomal storage disorders, mitochondrial disorders (1) and adrenoleukodystrophy in males. Despite extensive investigation however, the underlying diagnosis may remain elusive.

In this clinical context, the emergence of an additional symptom or sign may be helpful in signposting the clinician to a diagnosis. We present the case of a woman who had pre-existing diagnoses of epilepsy and leukoencephalopathy but in whom the development of premature ovarian failure triggered screening for mutations in the eukaryotic translation initiation factor 2B subunit genes (*EIF2B1-5*); a variety of *EIF2B1-5* subunit mutations have relatively recently been identified as causes of vanishing white matter (VWM) disease and ovarioleukodystrophy.

CASE HISTORY

Aged 19 years, our patient presented to another hospital with episodic neurological disturbance comprised of short-lived episodes of left-sided weakness preceded by paraesthesia. A single generalised tonic-clonic seizure was witnessed. A diagnosis of epileptic seizures was made and treatment commenced with sodium valproate and

levetiracetam. Neuroimaging changes consistent with leukoencephalopathy were noted and the patient was referred to our hospital for further investigation.

Perinatal history was unremarkable. In infancy and early childhood there had been mild developmental delay – she did not crawl and was identified as having mild learning difficulty. Menarche occurred in her early teenage years and menstrual cycles had been regular. Febrile convulsions were reported in infancy. She attended a mainstream school but left without attaining formal qualifications. Subsequently, she worked in the family bakery. The past medical history was unremarkable aside from the diagnosis of epilepsy and migraine.

Examination at that time revealed saccadic interposition of smooth pursuit, a postural upper limb tremor and a mild spastic quadriparesis. The patient was independent in activities of daily living and tremor improved following withdrawal of sodium valproate.

Investigations undertaken to identify the underlying cause of leukoencephalopathy (Figure 1) but which were unremarkable included an abdominal ultrasound, nerve conduction studies, visual evoked potentials and Goldmann perimetry. Plasma and urinary amino acids, urinary organic acids, very long chain fatty acids, muscle biopsy and fibroblast culture with filipin staining were all normal. Peripheral blood screening for polymerase gamma gene (*POLG*), progressive external ophthalmoplegia twinkle helicase gene (*C10orf2*) and cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) mutations was negative.

Aged 21 years and having been seizure free for 2.5 years, the menstrual cycle became irregular. Serum gonadotrophin levels confirmed premature ovarian failure. Karyotype analysis was normal. Hormone replacement therapy with the combined oral contraceptive pill was commenced but was rapidly complicated by the development of headaches, near continuous fortification spectra and elementary visual hallucinations ('coloured blobs') in the left visual field. There was a single generalised tonic-clonic seizure. EEG demonstrated rhythmic spike waves in the right posterior quadrant in keeping with the clinical suspicion of *epilepsia partialis continua*. Brain MRI confirmed restricted diffusion in the right occipital lobe (Figure 2). Initial treatment with benzodiazepines and increased levetiracetam was ineffective but seizure control was established following re-introduction of sodium valproate. Dual energy X-ray absorptiometry (DEXA) confirmed leukopenia with a low fracture risk. Her bone health is maintained vitamin D₃ supplementation with a plan for repeat DEXA in 10 years. Following withdrawal of hormone replacement therapy, lamotrigine monotherapy has been successful. There has been no progression of symptoms or signs over the following 2 years.

In view of the development of premature ovarian failure and the temporal relationship between the introduction of hormone replacement therapy and deterioration in control of migraine and epilepsy, an *eIF2B*-related disorder was considered. Blood samples were provided for whole gene screening by the patient and both parents. This confirmed compound heterozygote mutations of *EIF2B5*: maternal c.869>A, p.Arg299His and paternal c.913A>T, p.Met305Leu. Both mutations have been described in the context of vanishing white matter disease.

DISCUSSION

eIF2B is a 5-subunit guanine nucleotide exchange factor which supports the activation of eIF2 by GTP binding. Activated, GTP-bound eIF2 is essential for the initiation of eukaryotic translation as active eIF2 binds methionine-tRNA in the first steps of translation (2). *EIF2B* gene mutations may reduce guanine nucleotide exchange activity on eIF2-GDP with associated increased susceptibility to physiological stress. Given however that eIF2B is ubiquitously expressed and regulates essential eukaryotic function, it remains unclear why disease expression is restricted to CNS white matter and ovarian follicles; in cerebral white matter, hyaluronan is known to accumulate in eIF2B-related disorders and may inhibit glial maturation and function (3).

In the early 1990s, small paediatric series reported children with leukoencephalopathy who developed progressive ataxia and deteriorated in the context of head trauma or pyrexia (4) (5). Seizures and epilepsy were common. Progression of neurological disease was inexorable with the emergence of bulbar signs, optic atrophy and spastic quadriparesis. Death was reported to occur within 5 years of onset. Histopathology demonstrated normal grey matter and vacuolation of white matter with a paucity of astrocytes. Given the characteristic hypomyelination, the condition was initially described as childhood ataxia with cerebral nervous system hypomyelination (CACH) although the term 'vanishing white matter syndrome' has since become prevalent (6).

Mutations in *EIF2B1-5* were identified in VWM through genealogical study by haplotyping and radiation-hybrid mapping in patients known to have VWM (7); the

majority were found to have *EIF2B5* gene mutations although changes in *EIF2B2* were identified in others.

A case series (8) reported four women aged 15 - 29 with premature ovarian failure (primary amenorrhoea, delayed puberty or early menarche), neurological decline, and characteristic changes on brain MRI. The similarity of brain MRI changes to those described in CACH/VWM was noted and the term 'ovarioleukodystrophy' coined. In one case where ovarian tissue was examined histopathologically, dysgenesis was confirmed. In another, brain histopathology confirmed hypomyelination without evidence of demyelination in keeping with the findings reported in CACH. Sequencing of *EIF2B1-5* confirmed mutations in the *EIFB2*, *EIFB4* or *EIFB5* subunit genes in 7 out of 8 cases (9). At the time, none of these mutations had been described in CACH/VWM populations.

Another series (10) presented data from a cohort of 16 patients presenting with adult-onset eIF2B-related disorders. They reported a female preponderance (13:3 female to male) and a weak association of neurological decline with head injury or seizure (6 of 16). Reported outcomes were highly variable; one case was asymptomatic whilst significant disability (11 of 14) or death (2 of 16) were also reported over the period of follow up (mean 11.2 years).

Ovarioleukodystrophy is an extremely rare condition with fewer than twenty genetically-confirmed cases having been reported in the literature (11). Migraine and seizures have previously been reported and hormonal treatment has been associated with precipitating non-convulsive status in at least one other patient (12).

The diagnostic challenge facing the clinician investigating a patient with unexplained, progressive leukoencephalopathy is significant. We encourage practising neurologists and gynaecologists to be aware of the possibility of ovarioleucodystrophy and to liaise appropriately regarding cases where screening for *EIF2B1-5* gene mutations may be of diagnostic relevance.

Figure Legends

Figure 1: A - Coronal Fluid Attenuation Inversion Recovery (FLAIR) sequence brain MRI; B, C, D - Axial T2 Turbo Spin-Echo brain MRI (TSE). Cranial MRI demonstrated diffuse, symmetrical high T2 signal in the deep and subcortical white matter, without lobar predominance. The white matter was not swollen. There was symmetrical involvement of the extreme capsules but the external and internal capsules were spared. The basal ganglia, thalami and posterior fossa returned normal signal. The brain stem demonstrated volume loss as did the middle and superior cerebellar peduncles. Pallor in the middle cerebellar peduncles likely reflected Wallerian degeneration. The corpus callosum was also atrophic.

Figure 2: A - Diffusion Weighted Single Shot Axial brain MRI; B, C, D - Axial T2 Turbo Spin-Echo (TSE) brain MRI demonstrate high T2 signal in the swollen cortex of the right posterior temporal, occipital and parietal lobes, with decreased diffusion but normal flow void in the right posterior cerebral artery. Cranial CT Angiography (not shown) confirmed normal intracranial arterial circulation. The appearances were considered to reflect seizure activity, mitochondrial disease having been excluded. Interval MRI showed resolution of the right temporal, occipital and parietal cortical oedema.

Key points

Mutations in *EIF2B1-5* are a cause of vanishing white matter disease.

There is a spectrum of imaging changes associated with vanishing white matter disease; white matter vacuolation and loss are not prerequisites for the diagnosis.

The association of leukoencephalopathy and ovarian failure should prompt consideration of screening for eIF2B-related disorders.

Hormone replacement therapy may precipitate neurological deterioration and epileptic status in patients with eIF2B-related disorders.

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Competing Interests

The authors have no competing interests to declare.

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